REMARKS

In the Office Action dated December 15, 2005 claims 1-36 were examined with the result that all claims were rejected. In response, Applicant has canceled claims 2-5, 9, 12-15, 19, 22, 25-28, 32 and 35, and amended claims 1, 6-8, 11, 16-18, 24 and 29-31. In view of the above amendments and following remarks, reconsideration of this application is requested.

In the Office Action, claims 1-6, 8-16, 18-29, 31-33 and 35-36 were rejected under 35 USC §112, first paragraph, because the specification allegedly did not provide reasonable enablement for reducing the toxicity of all highly sterically hindered alcohols coupled to a retinoid. The Examiner states that Applicants have shown that the t-butyl moiety coupled to trans retinoic acid can reduce toxicity, and states that this one showing cannot be used to justify enablement of all compounds that fall into the category of retinoids or highly sterically hindered alcohols. The Examiner further supports this conclusion by stating that two of the exemplified compounds, i.e. pinacol and cholesterol coupled to all trans retinoic acid restored growth in vitamin D deficient rats, but "did not reduce toxicity."

In response, Applicant has limited all of the independent claims to the combination of a retinoid with a tertiary alcohol. The tertiary alcohol has a specific formula wherein the substituents R_3, R_4 and R_5 are either an alkyl group of 1-10 carbon atoms or an aryl group. Thus, Applicant believes that by limiting the claims to tertiary alcohols only, the exemplification of a t-butyl moiety coupled to all trans retinoic acid is sufficient to reasonably provide enablement for reducing the toxicity of retinoids that have been esterified with tertiary alcohols. The fact that the introduction of a highly sterically hindered group such as a tertiary alcohol at the free carboxyl group of the retinoid molecule markedly modulates the in vivo biological activity pattern of the resulting derivative was not appreciated previously. The realization of the importance of this specific modification, and the demonstration of its marked and highly beneficial

biological effects form the basis of this invention. Applicant refers the Examiner to the description contained at page 3, line 20 through page 4, line 25.

With regard to the Examiner's statement that the pinacol and cholesterol derivatives "did not reduce toxicity," Applicant refers the Examiner specifically to page 4, line 8 through page 4, line 13. It is stated there that the toxicity of the pinacol ester "was not tested," but it was surmised that it would be a very non-toxic form of retinoid derivative. Likewise, the cholesterol ester was not tested for toxicity, but again was believed to be a non-toxic form of retinoid. Thus, there is no support for the Examiner's statement that the pinacol and cholesterol derivatives "did not reduce toxicity" as stated in paragraph 2 of the Office Action. In any event, the Examiner should note that Applicant has canceled all of the claims directed toward the cholesterol derivative as the cholesterol derivative is not a combination of a retinoid and a tertiary alcohol as now required in the independent claims 1, 11 and 24.

Accordingly, Applicant requests the Examiner withdraw the §112, first paragraph rejection of the claims.

Before turning to the prior art rejections of record, Applicant would like to briefly summarize the amendments made to the claims. First, all of the claims directed toward secondary alcohols have been canceled. In addition, each of the independent claims 1, 11 and 24 have been amended to require the highly sterically hindered alcohol to be a tertiary alcohol having the specified formula wherein the substituents are either an alkyl group of 1-10 carbon atoms or an aryl group. That amendment to the independent claims required various dependent claims to be revised to have proper dependency. Finally, each of independent claims 1, 11 and 24 have been amended to add the step of formulating the ester derivative for oral or topical administration. Support for that amendment can be found in the specification as filed at page 28, lines 16-21 (oral administration) as well as at page 28, line 28 through page 29, line 2 (topical administration).

In the Office Action, claims 1-4, 10-14, 20, 24-27 and 33 were rejected under 35 USC §102(b) as being anticipated by Koyama et al JP-50076047. The Examiner states

that JP '047 teaches retinoid esters where the retinoid has been modified with an alcohol to its ester form, and the ester was found to be less toxic than non-modified retinoids. In addition, claims 1, 5-12, 15-25 and 28-36 were rejected under 35 USC §103(a) as being unpatentable over JP '047. The Examiner states that JP '047 teaches vitamin A modified with an alcohol to its ester form, and thus it would be obvious to one of ordinary skill in the art to extrapolate the process taught in JP '047 to a broader range of retinoids and/or alcohols. As a result, the Examiner believes JP '047 suggests that one skilled in the art could esterify any combination of retinoid and alcohol to result in a derivative with similar non-toxic properties.

In response, Applicant first notes that independent claims 1, 11 and 24 each have been limited to tertiary alcohols. Thus, since JP '047 only teaches the esterification of vitamin A with a secondary alcohol, the claims, as now amended, are clearly distinguishable over JP '047. As a result, Applicant believes the Examiner should withdraw the §102(b) anticipation rejection based on JP '047.

With regard to the §103(a) rejection, the Examiner should note that independent claims 1, 11 and 24 have also been amended to include the step of "formulating said ester derivative for oral or topical administration." Under normal circumstances, administration of vitamin A and/or other retinoid orally or topically can have very serious side effects because the compound is completely and immediately available upon administration. Toxic side effects such as weight loss, inanition, eye encrustation and bone loss may result. Other toxic side effects of orally administered retinoids include mucocutaneous toxicity and hyperlipidemia as well as teratogenic activity in pregnant mammals. These side effects have been a serious limitation to the use of oral retinoids in therapy. Topically applied retinoids also carry toxic results such as significant skin irritation. This is why it is important to note that in JP '047 the esters were administered interparenterally (i.p.), i.e. by injection, and not orally. Thus, a process whereby a retinoid can be made available orally in vivo more slowly and more continuously would avoid peaks and valleys in the availability of the retinoid thereby providing an effective in

vivo level of the compound over a more prolonged period of time and also avoiding or substantially reducing the toxicity that often results from the sudden availability of excess amounts of the compound.

JP '047 says nothing about the ability to make a retinoid available more slowly and more continuously by forming an ester derivative between the retinoid and a tertiary alcohol. One cannot readily assume that just because a vitamin A ester made with a secondary alcohol has "less i.p. toxicity than" the vitamin A acid itself that this means any and all ester derivatives would have less toxicity. Such a conclusion cannot be made merely from what is disclosed in JP '047.

Applicant's position is further supported by the Examiner's own §112, first paragraph, rejection made in the present Office Action. The Examiner states that Applicant's limited examples cannot support a claim to reduced toxicity of all highly sterically hindered alcohols and all retinoid compounds. How is it then that the limited number of examples in JP '047, all of which are esters formed from secondary alcohols, would render it obvious that esters formed from tertiary alcohols will reduce toxicity?

By amending the independent claims to call for formulating the derivative for, for example, oral administration, Applicant desires to further distinguish over i.p. administration. Oral administration is clearly more favorable than injections, and JP '047 only refers to i.p. toxicity. A problem that Applicant has solved is that by providing an ester derivative that is highly sterically hindered, it provides an effective retinoid compound that may be taken orally and cannot be easily destroyed by esterase enzymes in the gut of a patient because the ester derivatives are highly sterically hindered and thus prevent attack by the enzymes. This is what enables the compounds to be made available in vivo more slowly and more continuously to avoid the peaks and valleys of prior art compounds. There is nothing in JP '047 which would provide such a teaching to one skilled in the art.

Accordingly, Applicant believes the Examiner should withdraw the §103(a) rejection of the claims.

An effort has been made to place this application in condition for allowance and such action is earnestly requested.

Respectfully submitted,

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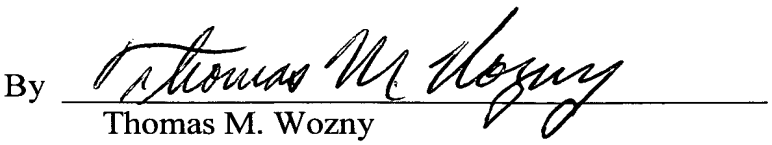
By 
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